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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/466,308	06/06/95	CLARK	S 118-6415/PCT

EXAMINER
MERTZ,T.

ART UNIT	PAPER NUMBER
1812	7

18M1/0625

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DATE MAILED: 06/25/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 4/12/96 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~0~~ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1 - 18 are pending in the application.
   Of the above, claims 9, 15, 17 - 18 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1 - 8, 14, 16 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

1. This is a Continuation of applicants earlier application. S.N. 08/287,019, filed under CFR 1.60; and is not a divisional application. Therefore, prosecution continues from the parent application.

2. Applicant's election of Group I in Paper No. 6 (4/12/96) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)).

Claims 1-8, 14 and 16 are pending and under consideration by the Examiner. Claims 9-13, 15, and 17-18 are withdrawn from further consideration by the Examiner as directed to a non-elected invention.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed i.e. a more specific title that would identify the protein (granulocyte macrophage-colony stimulating factor, GM-CSF).

4. Claims 1-4, 7-8, 14 and 16 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims

limited to "GM-CSF protein having the sequence shown in Figure 1". See M.P.E.P. §§ 706.03(n) and 706.03(z).

Claims 1-4, 7-8, 14 and 16 broadly encompass any "CSF protein". However, the specification only enables a protein of sequence shown in Figure 1, the polypeptide having specific characteristics. These properties may differ structurally, chemically and physically from other known proteins. It is well-known that the name of a protein is subject to change and often refers to more than one product. In the specification (see pg. 8, lines 12-13) applicants have defined a "CSF protein" as a protein from a primate source that exhibits CSF activity. Applicants also disclose that the present invention is particularly concerned with GM-CSF, more particularly human GM-CSF and ape GM-CSF (see pg. 3, last para). Furthermore, the term "CSF protein" as defined in the specification, encompasses modified CSF protein, allelic variations of CSF protein and CSF protein produced by a Met residue (see pg. 8, lines 13-15). Therefore, amino acid sequences that can deviate from the sequence shown in Figure 1, would be encompassed by the claims. However, the specification is enabled only for "the GM-CSF protein" having the amino acid sequence shown in Figure 1. Specifically, the instant specification does not identify those amino acid residues of the GM-CSF protein which are essential for its biological activity and structural integrity and those residues which are either expendable or substitutable. In the absence of

this information a practitioner would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional and substitutional mutation analysis of 127 amino acid residues before they could even begin to rationally design a functional GM-CSF polypeptide having other than a natural amino acid sequence. The disclosure of a single natural amino acid sequence is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims which encompass any and all GM-CSF polypeptides, including mutants thereof. Therefore, in order to avoid confusion over other patentably distinct proteins with the same name or similar discrete properties, it is suggested that the claims be amended to recite the enabled protein disclosed in the specification (Figure 1). It is also suggested that employing conventional claim language, the preamble to claim 1 read approximately as follows: "a recombinant GM-CSF protein having the amino acid sequence shown in Figure 1".

Claim 7 encompasses a CSF protein wherein "...one or more amino acids has been added, substituted or removed...". The specification does not teach modifications of the disclosed amino acid sequence of Figure 1. In fact, the specification fails to exemplify any such modifications. As written, the claims encompass peptides of various lengths, and truncated peptides. Given the scope of the various peptides within this term it is not evident that these resulting peptides would be functionally active and

possess the desired CSF activity. It is not predictable what a modification of the amino acid sequence would have on the mature protein. No modification of any kind of the mature protein has been demonstrated to have activity; therefore the aforementioned terms should not be used to describe other molecules that may have the activity as the instant protein. The specification does not disclose which amino acids may be substituted, deleted, or inserted without affecting the functional activity of the corresponding factor nor reveals residues essential for activity. It is not predictable if a modification in the amino acid sequence of the protein, would affect the corresponding polypeptide and if the modified polypeptide would have similar activity as the full-length polypeptide because modifications are expected to abolish activity. Therefore, without the guidance described above, the skilled artisan would have to obtain modifications of the amino acid sequence by random amino acid alterations; however randomly substituting or deleting amino acid residues can inactivate the corresponding protein. Absent structure/function studies it would require undue experimentation on the part of the artisan to obtain the various modifications of the polypeptide such that it would still possess the desired activity. Thus it would require undue experimentation on the part of the artisan to obtain modifications of the amino acid sequence of Figure 1, which possess the desired and favorable characteristic of the instant factor, in the absence

of sufficient information to predict the results with an adequate degree of certainty (Ex Parte Forman, 230 USPQ 546).

In view of the above discussion, the claims are not commensurate in scope with the specification but are directed to products that are broader than the supporting disclosure.

4. Claims 1, 6, 8, 14, 16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is rejected as unclear because of the recitation of "commencing with Ala.Pro ...". The claim would read more clearly if instead of the word "commencing", the specific number of the amino acid in Figure 1 was recited.

Claim 8 is rejected as vague and indefinite since the number of the claim on which it is dependent has not been recited.

Claim 1 is rejected as vague and indefinite for reciting "CSF" because the full meaning of the acronym "CSF" should be stated at its first use in any independent claim.

Claim 16 is rejected as vague and indefinite for being dependent on non-elected claim 12.

Claims 14 and 16 are indefinite for failing to recite a proper composition because a composition must recite at least 2 components, but these claims only recite 1 component. This

rejection can be obviated by amending the claim to recite "in a pharmaceutically effective carrier, vehicle or auxillary agent".

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this action:

> A person shall be entitled to a patent unless
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-6, 8, 14 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Golde et al. (1984). Golde et al. obtained a CSF and teach that the isolated protein was stimulatory to granulocyte-macrophage colonies (column 4, lines 20-57). The GM-CSF protein preparation disclosed in the Golde reference, obtained in a pharmaceutically acceptable carrier such as phosphate-buffered saline or distilled water, meets the limitations of the definition of a pharmaceutical composition. With respect to claim 16, the claim is a product-by-process claim and it does not appear that the

process imparts a patentable distinction to the product, CSF. Furthermore, a product made by any other process renders a product-by-process claim unpatentable. See MPEP 706.03(e). The reference does not disclose all of the characteristics recited in the claims, such as the particular amino acid sequences and the specific activity of the protein in the bone marrow assay. However, the protein of the reference appears to be the same species anticipated by the above claims. Since the cytokine disclosed by Golde et al. and the cytokine claimed by the applicant appear to be identical in view of their apparent molecular weight (molecular weight ~30,000 daltons) and activity, the cytokine in the prior art meets the limitations of the claimed factor. The distinguishing features, such as a amino acid sequence, would be inherently present in the species disclosed by the reference, even though these features are not specifically taught. The specific activity claimed in the instant invention would also be an inherent property of the reference protein. Therefore, the CSF produced by the process described in column 6 of the reference, when used as indicated in column 4 of the reference, would have anticipated the instantly claimed invention.

Claims 1-6, 8, 14 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Lusis et al. (1982). Lusis et al. disclose granulocyte and macrophage proliferation and differentiation that

is dependent upon the presence of GM-CSF and thus, anticipate production of granulocytes and macrophages by contacting the appropriate cells with GM-CSF produced as the translation product (see the paragraph bridging columns 1 and 2 on page 77, respectively). The GM-CSF protein preparation disclosed in the reference, obtained in a pharmaceutically acceptable carrier such as phosphate-buffered saline or distilled water, meets the limitations of the definition of a pharmaceutical composition. Even though the reference does not disclose the particular amino acid sequence of the protein, it appears to be the same species anticipated by the above claims. The cytokine disclosed by Lusis et al. and the cytokine claimed by the applicant are deemed to be identical in view of their molecular weight and activity (molecular weight ~30,000 daltons), and therefore, the cytokine in the prior art meets the limitations of the claimed factor. The distinguishing features, such as a amino acid sequence, would be inherently present in the species disclosed by the reference, even though these features are not specifically taught. The specific activity and amino acid sequence claimed in the instant invention would be an inherent property of the reference protein. Therefore, the CSF produced as a translation product in the reference, would have anticipated the instantly claimed invention.

Claims 1-3, 8, 14 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Bleackley et al. (1983). The reference discloses granulocyte and macrophage proliferation and differentiation that is dependent upon the presence of GM-CSF and thus, anticipates production of granulocytes and macrophages by contacting the appropriate cells with GM-CSF produced as the translation product (see page 3034, lines 12-17). The GM-CSF protein preparation disclosed in the reference, obtained in a pharmaceutically acceptable carrier such as phosphate-buffered saline or distilled water, meets the limitations of the definition of a pharmaceutical composition. The specific activity claimed in the instant invention would be an inherent property of the reference protein. ion would be an inherent property of the reference protein. Though the reference discloses murine GM-CSF, the protein disclosed in the Bleackley reference is deemed to be the same as that disclosed in the instant application because the claims are silent as to the species of the GM-CSF protein. Therefore, the CSF produced as a translation product in the reference, would have anticipated the instantly claimed invention.

Claims 1-3, 8, 14 and 16 are rejected under 35 U.S.C. § 102(a) as being anticipated by Gough et al. (1984).

Gough et al. discloses the nucleotide sequence of the cDNA clone encoding recombinant murine GM-CSF, and the amino acid

sequence of murine GM-CSF and a method of producing GM-CSF protein by expressing the protein in prokaryotic cells (*E. coli*) into which has been transformed a vector having inserted therein a gene coding for said GM-CSF protein (see abstract, pg. 763; pg. 766, column 2, Figure 5; pg. 764, column 2, legend to Figure 1). The GM-CSF protein preparation disclosed in the reference, obtained in a pharmaceutically acceptable carrier such as phosphate-buffered saline or distilled water, meets the limitations of the definition of a pharmaceutical composition. The specific activity claimed in the instant invention would be an inherent property of the reference protein. Though the reference discloses murine GM-CSF, the protein disclosed in the Gough reference is deemed to be the same as that disclosed in the instant application because the claims are silent as to the species of the GM-CSF protein. Therefore, the GM-CSF protein disclosed in the Gough reference is deemed to meet the limitations of a recombinant GM-CSF protein.

It is impossible for the Examiner in charge of this application to physically compare the claimed protein and the protein of the prior art. Applicant bears the burden of providing evidence which distinguishes the claimed protein from that of the references (see Ex parte Gray, 10 USPQ 2d 1922 (BPAI, 1989). A preferred means of providing this evidence is for the applicant to submit a side by side comparison with the protein of the prior art

and the claimed protein, which demonstrate any material differences and show them to be distinct.

All the above references disclose to the public that which is claimed in this application. In the case of the Lusis et al., and Bleackley et al. references, public disclosure was made more than one year prior to the filing of this application, therefore the issuance of a patent thereon is barred. No distinctions can be seen between the GM-CSF protein taught in any of the cited references and the GM-CSF protein claimed in this application.

No claims are allowed.

6. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Prema Mertz whose telephone number is (703) 308-4229. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:00PM (Eastern time).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Garnette D. Draper, can be reached on (703) 308-4232.

Papers related to this application may be submitted to Group 1800 in Crystal Mall 1 by facsimile transmission, in conformity with the notice published in the official Gazette, 1096 0G 30 (November 15, 1989). The FAX phone number for Art Unit 1812 is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Prema Mertz Ph.D. PM
Examiner
June 13, 1996

JOHN ULM
PRIMARY EXAMINER
GROUP 1800